UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

Note to Reader

Background: As part of its effort to involve the public in the implementation of the Food Quality Protection Act of 1996 (FQPA), which is designed to ensure that the United States continues to have the safest and most abundant food supply. EPA is undertaking an effort to open public dockets on the organophosphate pesticides. These dockets will make available to all interested parties documents that were developed as part of the U.S. Environmental Protection Agency's process for making reregistration eligibility decisions and tolerance reassessments consistent with FQPA. The dockets include preliminary health assessments and, where available, ecological risk assessments conducted by EPA, rebuttals or corrections to the risk assessments submitted by chemical registrants, and the Agency's response to the registrants' submissions.

The analyses contained in this docket are preliminary in nature and represent the information available to EPA at the time they were prepared. Additional information may have been submitted to EPA which has not yet been incorporated into these analyses, and registrants or others may be developing relevant information. It's common and appropriate that new information and analyses will be used to revise and refine the evaluations contained in these dockets to make them more comprehensive and realistic. The Agency cautions against premature conclusions based on these preliminary assessments and against any use of information contained in these documents out of their full context. Throughout this process, If unacceptable risks are identified, EPA will act to reduce or eliminate the risks.

There is a 60 day comment period in which the public and all interested parties are invited to submit comments on the information in this docket. Comments should directly relate to this organophosphate and to the information and issues available in the information docket. Once the comment period closes, EPA will review all comments and revise the risk assessments, as necessary.

These preliminary risk assessments represent an early stage in the process by which EPA is evaluating the regulatory requirements applicable to existing pesticides. Through this opportunity for notice and comment, the Agency hopes to advance the openness and scientific soundness underpinning its decisions. This process is designed to assure that America continues to enjoy the safest and most abundant food supply. Through implementation of EPA's tolerance reassessment program under the Food Quality Protection Act, the food supply will become even safer. Leading health experts recommend that all people eat a wide variety of foods, including at least five servings of fruits and vegetables a day.

Note: This sheet is provided to help the reader understand how refined and developed the pesticide file is as of the date prepared, what if any changes have occurred recently, and what new information, if any, is expected to be included in the analysis before decisions are made. **It is not meant to be a summary of all current information regarding the chemical.** Rather, the sheet provides some context to better understand the substantive material in the docket (RED chapters, registrant rebuttals, Agency responses to rebuttals, etc.) for this pesticide.

Further, in some cases, differences may be noted between the RED chapters and the Agency's comprehensive reports on the hazard identification information and safety factors for all organophosphates. In these cases, information in the comprehensive reports is the most current and will, barring the submission of more data that the Agency finds useful, be used in the risk assessments.

Jack E. Housenger, Acting Director
Special Review and Reregistration Division

MEMORANDUM

SUBJECT: The HED Chapter of the Reregistration Eligibility Decision Document (RED) for Fenitrothion

FROM: John C. Redden, M.S.
Chemical Coordination Branch
Health Effects Division (7509C)

THRU: Esther Saito, Branch Chief
Chemical Coordination Branch
Health Effects Division (7509C)
and
Penelope Fenner-Crisp, Ph.D, Director
Health Effects Division (7509C)

TO: Lois Rossi, Chief
Reregistration Branch
Special Review and reregistration Division (7508W)

Please find attached the Human Health Assessment for the Fenitrothion Reregistration Eligibility Decision Document (RED). This chapter includes the Hazard Assessment from J. Redden in TBI (ATTACHMENT I), the Occupational/Residential Exposure Assessment from S. Bacchus in OREB (ATTACHMENT II), the Product and Residue Chemistry Assessments from B. Cropp-Kohlligian in CBII (ATTACHMENT III), and the Dietary Risk Analysis from S. Schaible in DRES (ATTACHMENT IV).

Fenitrothion [O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate] is a cholinesterase inhibiting insecticide/acaricide. Fenitrothion is labeled for use on terrestrial and greenhouse non-food crops and for indoor residential settings. There are no registered food uses in the U.S.

The toxicological data base for fenitrothion is adequate and will support reregistration eligibility. Two studies are outstanding. The inhalation acute study is considered confirmatory because testing of end-use products will address labeling concerns. The ocular toxicity study was not a part of the required data base for reregistration eligibility, but was requested in a Data Call In

(DCI). The study is outstanding and is considered a data gap.

There is no consumption estimate for "wheat gluten" in the DRES system. Instead of assuming the consumption estimate of "wheat flour" for "wheat gluten", which would have resulted in considerable overestimation of exposure and risk, DRES used production data from USDA, the 1992 census estimate of the U.S. population, and a "percent of wheat gluten imported from Australia" estimate to derive a consumption value specific to wheat gluten.

Using this consumption value and the recommended residue of 15 ppm, exposure to the U.S. population was estimated at 0.000043 mg/kg bwt/day, which represents 3% of the RfD. If one assumes that wheat gluten is consumed by children at the same ratio to the overall U.S. population's consumption that wheat flour is, the estimated exposure for children one through six is 0.000097 mg/kg/bwt/day, or 8% of the RfD. If the existing tolerance of 30 ppm is used, these exposure and risk estimates are doubled (7% of the RfD for the overall U.S. population, 15% of the RfD for children 1 through 6).

The chemistry data base is adequate and supports reregistration. The Residue Chemistry Science Assessment addresses the adequacy of available data to support the food additive tolerance for residues of fenitrothion in wheat gluten imported from Australia. At this time, no additional data are required, but the Agency reserves the right to require additional data, if new food uses are requested. The HED Metabolism Committee has determined that regulation of the tolerance for residues in wheat gluten should be in terms of the parent compound only.

HED has a concern for short term, intermediate term, and chronic exposure to fenitrothion based on the results of the acute neurotoxicity study, the 90-day inhalation study, and the 21-dermal study. In the acute neurotoxicity study in rats, the dose level of 12.5 mg/kg is considered the NOEL for both Sexes. At 50 mg/kg (both sexes) as many as 16 FOB parameters were affected (the most prominent being tremors, ataxia and gait incapacity); in addition, body temperature and motor activity were decreased. In the 90-day inhalation study, a NOEL of 0.2 μg/l was determined on the basis of brain cholinesterase inhibition in females. In the 21-dermal study, the Systemic NOEL equals 3 mg/kg/day, and the Systemic LOEL equals 10 mg/kg/day based on inhibition of plasma cholinesterase (40%) and brain (20%) cholinesterase in females. The dermal NOEL was not determined. The dermal LOEL equals 3 mg/kg/day based on dermal irritation and desquamation of the epidermis.

The acute neurotoxicity endpoint is appropriate for dietary risk assessment. However, because Australian gluten is probably mixed with other gluten, there is not likely to be an acute risk from gluten consumption. Calculations using the RfD indicate minimal risk; since the acute NOEL is 100-fold greater than the NOEL used to establish the RfD, there is no concern for acute dietary exposure.

Workers may be exposed short term, intermediate term and chronically. In particular, based on these endpoints, the following post-application exposures have been identified as areas of greatest concern: Residential exposure after mosquito control treatments and greenhouse worker exposure after treatment of ornamental plant beds and potted plants. There is also a concern due to exposure after contact with treated ornamental plants and foliage (outdoor).

Exposure data required by the Registration Standard were:

- Safe Use of Pesticides; Third Report of the World Health Organization (WHO) Expert Committee on Vector Biology and Control--Fenitrothion Aspects Excerpted From WHO Technical Report Series 634 (EPA MRID 404089-28),

- Determination of Urinary Metabolites as a Measurement of Exposure of Spraymen and Householders to Fenitrothion and Malathion in Haiti--Presented at the 23rd Meeting of the Collaborative International Pesticide Analytical Council/Sponsored by the Vector Biology and Control Division, Bureau of Tropical Diseases, Centers for Disease Control (EPA MRID 404089-29), and

- Exposure of Mixer/Loader/Applicators to Pestroy (Fenitrothion) Insecticide Applied to Ornamentals by Hand-Held Spraygun Equipment (EPA MRID 410963-01). [Note: An addendum was submitted for this study (i.e., MRID 429703-01, Representative Chromatograms and Analytical Data To Supplement Study of Exposure of Mixer/Loader/Applicators to Pestroy (Fenitrothion) Insecticide Applied by Hand-Held Spraygun Equipment, 1988.]

The studies submitted to the Agency were all unacceptable because of the study design, the level of detail provided therein, and the associated lack of quality control/quality assurance regimens during the biological monitoring of workers. Additionally, the Mixer/Loader/Applicator exposure study is unacceptable (MRID#s 410963-01, 429703-01) because of several major inadequacies. Based on toxicological concerns and the potential

for significant exposure, these are still considered data gaps. Nonetheless, limited information from these studies indicate that for these following scenarios, the MOEs are less than 100:

- Residential exposure after mosquito control treatments
- Open mixing liquids (mixer/loader);
- Low pressure handwand application (applicator);
- Overhead boom sprayer application (applicator);
- High Pressure handwand application (applicator);
- Mixing and application with low pressure handwands (mixer/loader/applicator);
- Knapsack/backpack (mixer/loader/applicator); and
- Mixing and application with high pressure handwand (mixer/loader/applicator).

The Restricted Entry Interval (REI) should be at least 24-hours since fenitrothion is a Toxicity Category II dermal toxicant. The Agency recommends continuing to require a 24-hour REI for all use sites within the scope of the WPS until adequate post-application exposure data are submitted.

Except for homeowner users, the Agency is requiring PPE for applicators and other handlers as well as early entry workers consistent with the PPE level required for pesticides classified as Toxicity Category II for acute dermal toxicity (40 CFR Part 156, the Worker Protection Standard). For further information see PR Notices 93-7 and 93-11. WPS worksheets provided by OREB are attached. The registrant may be able to suggest other risk mitigation options.

Attachments
cc:
B. Cropp-Kohlligian (CBRSII)
S. Schaible (DRES)
S. Bacchus (OREB)
J. Redden (CCB)

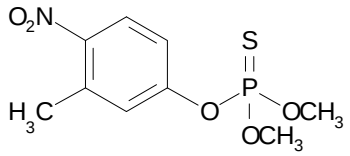
SCIENCE ASSESSMENTS OF FENITROTHION

A. PRODUCT CHEMISTRY ASSESSMENT

All pertinent product chemistry data requirements are satisfied for the fenitrothion 95% T registered to Sumitomo Chemical America, Inc. (EPA Reg. No. 39398-4).

1. Identification of the Active Ingredient

Fenitrothion [O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate] is a cholinesterase inhibiting insecticide/acaricide. The molecular structure of fenitrothion is provided below:



Empirical Formula: $C_9H_{12}NO_5PS$
Molecular Weight: 277.2
CAS Registry No.: 122-14-5
Shaughnessy No.: 105901

The technical fenitrothion is a yellowish-brown oil which decomposes at 140-145°C (at 0.1 mmHg) and has a density of 1.32-1.34. Its solubility in water at 20°C and 30°C is 5 mg/kg and 14 mg/kg, respectively. Fenitrothion solubility at 22-25°C in methanol and acetone is >50% w/w and in hexane is <10% w/w.

B. HUMAN HEALTH ASSESSMENT

1. Toxicology Assessment

The toxicological data base is adequate and will support reregistration as a non-food use pesticide. The following data gaps exist and are required to maintain the continued registration of fenitrothion following reregistration: 1) 81-3 Acute Inhalation LC50 Study; and 2) six month ocular toxicity study in dogs.

a. Acute Toxicity

The acute toxicity on fenitrothion are summarized below:

TEST	RESULT (mg/kg)	CATEGORY
81-1: Oral LD50 MRID Nos. 232483 & 00061091 Sumithion Technical (97.2%)	LD50 = 330 mg/kg (M), LD50 = 800 mg/kg (F)	II
81-2: Dermal LD50 MRID Nos. 232483 & 00007959 Sumithion Technical (97.2%)	LD50 = 890 mg/kg (M), LD50 = 1200 mg/kg (F)	II
81-3: Inhalation LC50* MRID No. 00062977 Sumithion 8-E (77% a.i.)	LC50 = 5.0 mg/l	II
81-4: Eye effects MRID No. CRSU; 0002 Sumithion 8-E (77% a.i.)	PIS = 0.1/110 at 72 hrs., PIS = 0/110 at 7 days.	II
81-5: Dermal Irritation MRID No. CRSU;0003 Sumithion 8-E (77% a.i.)	PIS = 2.75 (mild irritant)	II
81-6: Dermal Sensitization MRID No. 61091 Sumithion Technical (97.2%)	Animals treated with 0.1 ml of 5% and 1% sumithion - results negative	N/A
81-8 Neurotoxicity-acute delayed MRID No. 232483 and 00069955; Species: hen Sumithion Technical (97.2%)	Mortality - 3/16 after first administration; 3/13 after second administration; Negative at 500 mg/kg	N/A
81-8SS Neurotoxicity Screen MRID No. 426669-01; Species: rat Fenitrothion Technical (94.3%)	NOEL and LEL = 12.5 and 50 mg/kg for males in the study. A NOEL could not be determined for the females	N/A

*: Unacceptable

The 81-3 Acute Inhalation LC50 Study has numerous deficiencies and must be repeated.

The Acute studies listed below were <u>not</u> conducted with the Technical grade material:

1) 81-3 Acute Inhalation LC50 Study;
2) 81-4 Primary Eye Irritation; and
3) 81-5 Primary Dermal Irritation.

b. Subchronic Toxicity

Guideline requirement 82-1, 90-day feeding - Rodent, is satisfied by the two year chronic feeding/oncogenicity study (MRID No. 00071965, see d. Chronic Toxicity, Carcinogenicity). Guideline requirement 82-1, 90-day feeding-Nonrodent (Dog), is satisfied by the one-year dog feeding study MRID No. 254868.

In a 21-day dermal study (Guideline requirement 82-2) MRID No. 420583-01 Fenitrothion (93.7%) was applied to the skin of New Zealand white rabbits. The dose levels were 0, 3, 10, 50 and 250 mg/kg/day. The Systemic NOEL equals 3 mg/kg/day, and the Systemic LOEL equals 10 mg/kg/day based on inhibition of plasma cholinesterase (40%) and brain (20%) cholinesterase in females. The dermal NOEL was not determined. The dermal LOEL equals 3 mg/kg/day based on dermal irritation and desquamation of the epidermis.

In Guideline requirement 82-4, 90 day inhalation study, MRID No. 408910-01, Crl (WI) BR strain rats were exposed to 0, 0.2, 1.0, or 10 µg/l of Sumithion Technical (94.5%). At 10 µg/l, plasma cholinesterase activity in males and RBC cholinesterase activity in both males and females was inhibited. A NOEL of 0.2 μg/l was determined on the basis of brain cholinesterase inhibition in females.

c. Chronic Toxicity and Carcinogenicity

The following two studies, when combined, satisfy data requirement 83-5 (or 83-1a and 83-2a) for chronic toxicity and carcinogenicity testing in the rat.

A two year chronic feeding/oncogenicity study (§ 83-1(a) & § 83-2(a)), MRID No. 00071965, was conducted in the Charles River/CD strain rat. The compound was administered in the diet at doses of 0, 0.5, 1.5 or 5 mg/kg/day (0, 10, 30 or 100 ppm). The cholinesterase LEL equals 10 ppm (LDT) (brain and plasma).

A 22 month chronic feeding/oncogenicity study (§ 83-1(a) and 83-2(a)), MRID No. 40420501, was conducted in the Wistar strain rat. The compound was administered in the diet at doses of 0, 0.125, 0.25, or 0.5 mg/kg/day (0, 2.5, 5.0 or 10 ppm). The Systemic NOEL is greater than 2.5 ppm. The cholinesterase NOEL equals 2.5 ppm; the cholinesterase LEL equals 5.0 ppm (plasma).

At 10 ppm, RBC cholinesterase was reduced.

A two year chronic feeding/oncogenicity study(§ 83-1(a) & 83-2(b)), MRID Nos. 419252-01, 425077-01 and 415077-04, was conducted in B6C3F1 mice. The compound was administered in the diet at 0, 3, 10, 100, or 1000 ppm (0, 0.45, 1.51, 13.07, or 144.32 mg/kg/day for the females, and at 0.37, 1.45, 12.62, or 134.28 mg/kg/day for the male). The study was conducted at adequate dosage based on a 26-29% suppression in body weight gain at 1000 ppm (both sexes) and a depression of cholinesterase observed at 100 and 1,000 ppm (both sexes). The Systemic NOEL equals 3 ppm (0.45 mg/kg/day); Systemic LEL equals 10 ppm (1.45 mg/kg/day) based on decreased body weight gains, decreased RBC, brain, and plasma cholinesterase activity.

A one year feeding study (§ 83-1(a)), MRID No. 254868, was conducted in beagle dogs. The compound was administered in the diet at 0, 5, 10, or 50 ppm (0, 0.125, 0.25, or 1.25 mg/kg/day). The cholinesterase NOEL equals 5 ppm; cholinesterase LEL equals 10 ppm (plasma cholinesterase inhibited); Systemic NOEL equals 5 ppm; and Systemic LEL equals 10 ppm (increased incidence of abdominal lymph node hemorrhage).

The chemical was classified by the RfD committee on the basis of its carcinogenic potential in **Group E** - evidence of non-carcinogenicity for humans.

d. Developmental and Reproductive Toxicity

A developmental toxicity study (Guideline requirement 83-3(a)) MRID No. 406040-02 was conducted with pregnant Sprague-Dawley rats which were administered 0, 3, 8 or 25 mg/kg/day Fenitrothion from day 6 through day 15 of gestation. The Maternal NOEL equals 8 mg/kg/day, and the Maternal LEL equals 25 mg/kg/day based on a decrease in the percentage body weight gain and the absolute body weight (days 11 through 19 of gestation), decreased mean corrected terminal body weight and tremors in 9 of the 24 females. The Developmental NOEL equals 8 mg/kg/day, and the Developmental LEL equals 25 mg/kg/day based on an increased incidence of fetuses and litters with one full and one rudimentary 13th rib.

A developmental toxicity study (§ 83-3(b)) MRID Nos. 264497, 00162548, and 404306-01 was conducted with HRA: (NZW) SPF strain rabbits. The compound was administered by gavage at doses of 0, 3, 10 or 30 mg/kg. The Maternal NOEL equals 10 mg/kg/day, and the Maternal LEL equals 30 mg/kg/day (increased mortality, abortion, tremors, ataxia and dyspnea and reduced body weight gain). The Developmental NOEL equals 30 mg/kg/day (HDT).

A 2-generation reproduction study MRID No. 416890-01 and 426688-01 was conducted with Sprague-Dawley (Crl:COBS CD SD BR) rats. The compound was administered by gavage in a corn oil vehicle at doses of 0, 10, 40, or 120 ppm (Male: 0.68, 2.74, or 8.40 mg/kg/day; Female: 0.77, 3.19 or 10.37 mg/kg/day). The parental toxicity NOEL equals 40 ppm based on the following observations: 1) decreased food consumption, body weight and weight gain in both generations and sexes at 120 ppm. The parental toxicity LEL equals 120 ppm. The reproductive toxicity NOEL equals 40 ppm based on the following observations: 1) decreased fertility in the F_0; and decreased numbers of implantation sites, decreased viability and lactation. The reproductive LEL equals 120 ppm.

e. Mutagenicity

A § 84-2 Gene Mutation Assay (Ames Assay) MRID No. CRSU;0005 was conducted using Sumithion Technical (98.6%). Doses ranged from 100 to 2000 µg/plate. Fenitrothion is mutagenic in Salmonella typhimurium strain TA100 with S-9 activation, but not mutagenic in the nitroreductase deficient strain TA100 nit- with S-9 activation. The selected dose range was adequate for demonstrating a mutagenic effect in TA100, but the results indicate a false-positive response associated with bacterial nitroreductase activity. Since mammals lack the type of nitroreductase found in bacteria, Sumithion is not considered to be a potential mammalian mutagen.

A § 84-2 Chromosome Aberration in vitro study with CHO cells MRID No. 407892-01 was conducted using Fenitrothion. Fenitrothion was found to be negative in Chinese hamster cells treated up to cytotoxic and insoluble levels, 300 µg/ml with and without S9 activation.

An Unscheduled DNA Synthesis Assay (Other Genotoxic Effects § 84-4) with rat hepatocyte study MRID No. 407892-02 was conducted using Fenitrothion (96.7%). Fenitrothion was found to be positive for inducing unscheduled DNA synthesis (UDS) in primary rat hepatocyte cultures, but only at the HDT, 30 µg/ml, a cytotoxic dose (60-70% relative cell viability).

f. Metabolism

A metabolism study (Guideline requirement 85-1) conducted with the rat is available (MRID No. 00069960 & 404089-06). C^{14} Sumithion administered to male and female Wistar rats, male and female rabbits, or male beagle dogs as a single dose of 15 mg/kg was absorbed rapidly and excreted nearly to completion in 48 hours with approximately 90% and 5% of the excreted dose eliminated in the urine and feces, respectively. Expired air from rats contained no

radioactivity; C^{14} levels in the tissues were not measured. There were no sex- or species-related differences in the total excretion. A single oral dose (105 mg/kg) in rats with labeled Sumithion for 5 days did not alter the excretion profile. Seventeen metabolites were isolated in the urine of rats, rabbits, and dogs, but only eight were identified. The parent compound was not detected in the urine of any animal. In the feces, no metabolites other than those found in the urine were present.

The urinary metabolites of fenitrothion have been identified in the male and female rat. The fecal metabolites have been identified in the male but not the female rat. The major metabolic routes appear to be (1) the demethylation of the phosphate moiety, (2) desulfuration of the phosphate moiety and (3) the hydrolysis of the phosphate moiety from the phenyl moiety as reflected by the types of metabolites found in the urine and feces. The pattern of distribution and elimination of fenitrothion in male and female rats was similar regardless of receiving a single nontoxic dose (15 mg/kg) exposure, a single toxic dose (105 mg/kg) exposure or repeated nontoxic dose exposure (15 mg/kg every other day for 5 times, and then treated with 15 mg/kg of radiolabeled fenitrothion). Fenitrothion is excreted in the urine (95% of total dose) and in the feces (about 5% of the remaining dose) within 7 days of exposure. Fenitrothion and/or its metabolites were not detected in the expired air of either male or female rats. No major sex differences were observed in the distribution, metabolism or the excretion of fenitrothion.

g. Ocular effects

An Acute Ocular Toxicity Study MRID No. 412496-01 was conducted with Sprague-Dawley (SD) (Crj:CD) rats using Fenitrothion (94.5%). Doses were administered by oral gavage at the following levels: 0, 20, or 200 mg/kg for males, and 0, 40, or 400 mg/kg for females. The cholinesterase NOEL could not be determined. The cholinesterase LOEL was less than 20 and 40 mg/kg (LDT) based on erythrocyte cholinesterase inhibition in male and female rats respectively. The Ocular NOEL is greater than 200 mg/kg for males, and 400 mg/kg for females, based on lack of changes clearly related to treatment in electroretinography and ophthalmic examination of the anterior portions of the eye. The Ocular LOEL was not determined. No residual effect was observed on the ERG following doses which produced signs of toxicity and were accompanied by depression of plasma and erythrocyte cholinesterase activity. No indications of ocular toxicity were observed.

A 13-week subchronic study MRID No. 412496-02 was conducted with Sprague-Dawley (SD) (Crj:CD) rats using Fenitrothion (94.5%).

Doses were administered in the feed at the following doses: 0, 2.5, 5, 10 or 30 ppm (Males: 0, 0.14, 0.282, 0.570 or 1.70 mg/kg/day; Females: 0, 0.169, 0.331, 0.648, or 1.96 mg/kg/day). The cholinesterase NOEL equals 5 ppm based on a statistically significant inhibition of plasma cholinesterase in female rats to approximately 54% of the control activity levels. In addition, at 30 ppm, statistically significant inhibition of plasma, erythrocyte and brain cholinesterase was observed in female rats, and of plasma and erythrocyte cholinesterase in male rats.

No effect was observed on the ERG at the end of dosing either in comparison to pretreatment values or in comparison to concurrent control values. The high dose showed depression of plasma, erythrocyte and brain cholinesterase at the end of the study. The study showed no evidence of ocular toxicity.

A six month ocular toxicity study in dogs, requested in a Data Call In (DCI), is outstanding and is considered a data gap. This requirement is supported by the Japanese study of Ishikawa and Miyata (1980), which demostrated a statistically significantly increase of myopia in dosed dogs.

i. Reference Dose (RfD)

The Committee concluded that an RfD should be established based upon a NOEL of 0.125 mg/kg/day for Systemic effects (histopathological changes in lymph nodes) and plasma cholinesterase inhibition observed at 0.25 mg/kg/day in a long-term feeding study in dogs. An Uncertainty Factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. **On this basis the RfD was calculated to be 0.0013 mg/kg/day.**

The Joint FAO/WHO Meeting On Pesticide Residues (JMPR) reports an ADI of 0.005 mg/kg bw (1988).

2. Exposure Assessment

a. Dietary Exposure

a-1. §171-4 (a): Plant Metabolism

The qualitative nature of the residue in wheat grain is understood adequately based upon the available rice metabolism/degradation data. The submitted data indicate that fenitrothion per se, desmethyl fenitrothion, and p-nitrocresol are the major components of the residue. Additional metabolites/degradants retaining the aryl phosphate or

phosphorothioate moiety which were present in very small amounts (i.e., collectively <3% of the TRR in rice grain) were fenitrooxon, fenitrothion S-isomer, desmethylfenitrooxon, and desmethylfenitrothion S-isomer. The HED Metabolism Committee has determined that regulation of the tolerance for residues in wheat gluten should be in terms of the parent compound only. No additional data are required.

a-2. §171-4 (b): Animal Metabolism

Fenitrothion is not registered for use on any domestic crop; therefore, residues of fenitrothion are not expected to enter the diet of food animals. In the event that future registrations for use of fenitrothion on plant commodities used for animal feeds are approved, or regulations covering importation of animal products from countries in which fenitrothion is registered for use are established, additional animal metabolism studies may be required.

a-3. §171-4 (c): Residue Analytical Methods - Plants

A GLC method, which was published and described in the Journal of Agriculture and Food Chemistry 17:271-276, has been deemed adequate for data collection and enforcement purposes. A successful EPA method tryout (MTO) was conducted (Zee, 1979; no MRID assigned) on wheat gluten using the preferred GLC method. Although certain inconsistences in the EPA method tryout (MTO) reports were identified, they are irrelevant to the method's adequacy for data collection and enforcement purposes. The method will be submitted for publication in PAM Vol. II.

Residues of fenitrothion have been subjected to multiresidue protocols required in the 40 CFR 158.125(b)(15) and published in the Addendum to Pesticide Assessment Guidelines Subdivision O - Residue Chemistry Data Requirements Multiresidue Protocols. Fenitrothion is recovered completely (>80%) using FDA Multiresidue Protocols D (232.4) and E, fatty and nonfatty (211.1 and 212.1) is also recovered completely using FDA Multiresidue Protocol D (232.4).

No additional data are required.

a-4. §171-4 (d): Residue Analytical Methods - Animals

Fenitrothion is not registered for use on any domestic crop; therefore, residues of fenitrothion are not expected to enter the diet of food animals. In the event that future registrations for use of fenitrothion on plant commodities used for animal feeds are approved, or regulations covering importation of animal products

from countries in which fenitrothion is registered for use are established, adequate residue analytical methods may be required for data collection and regulatory purposes.

a-5. §171-4 (e): Storage Stability

The available storage stability data indicate that residues of fenitrothion are stable under frozen (-18°C) storage conditions in/on wheat and wheat gluten for up to 147 and 174 days, respectively, which is adequate to support the available residue data. No additional data are required.

a-6. §171-4 (j): Magnitude of the Residue in Animals

Fenitrothion is not registered for use on any domestic crop; therefore, residues of fenitrothion are not expected to enter the diet of food animals. In the event that future registrations for use of fenitrothion on plant commodities used for animal feeds are approved, or regulations covering importation of animal products from countries in which fenitrothion is registered for use are established, additional animal feeding studies may be required.

a-7. §171-4 (k-l): Magnitude of the Residue in Plants

All data requirements for the magnitude of the residue in plants have been evaluated and deemed adequate with the assumption that the magnitude data which have been submitted to the Agency adequately reflect the maximum registered use rate of fenitrothion on stored wheat in Australia. All data requirements for the magnitude of the residue in wheat gluten as a result of the postharvest application of fenitrothion to stored wheat in Australia have been evaluated and deemed adequate. No additional data are required.

b. Residential and Occupational Exposure

Fenitrothion (O,O-dimethyl O-(4-nitro-m-tolyl) phosphorothioate) is an organophosphate insecticide/acaricide. End-use products include a 40% wettable powder (WP), a 76.8% ready-to-use liquid, and emulsifiable concentrate (EC) formulations. The wettable powder is not marketed in water soluble packets. Two of the EC formulations contain 76.8% active ingredient while the remaining formulation contains 45% fenitrothion.

Fenitrothion is labelled for use on terrestrial and greenhouse non-food crops and for indoor residential settings. Applications can be made using ground or hand held equipment along with various

types of sprayers typical of those used in indoor settings.

Outdoor terrestrial and greenhouse use sites include: ornamental/shade trees, ornamental herbaceous plants, ornamental nonflowering plants, and ornamental woody shrubs and vines. These two use groups are considered together for the purposes of this RED because most of the application equipment can be used both in greenhouses and outdoors. Furthermore, the application rates are the same regardless of whether the site is a greenhouse or a commercial tree lot. Therefore, the same daily exposure is likely for outdoors or a greenhouse.

Applications are intended to control a variety of insect pests such as, but not limited to, the spruce budworm, aphids and southern pine beetles. Application methods for these scenarios include: basal bark treatments, broadcast applications, and spot treatments. Basal bark treatments are to be repeated every 90 days while spot treatments and broadcast applications are to be repeated every 7 days. Applications are made to run-off on various target plants using up to 100 gallons of spray solution per acre at spray solution concentrations ranging from approximately 0.12% up to 2% active ingredient (w/v).

Indoor residential use sites include household and domestic indoor non-food handling areas. Fenitrothion is used indoors to control mosquitoes and, consequently, malaria disease vectors. Applications are atypical as they are general surface area treatments of wall surfaces and not flooring (e.g., broadcast or typical crack and crevice treatments). These treatments are limited to mosquito control and can be made at rates up to 0.88 lb ai/2153 ft^2 of wall space in 2.1 gallons of spray solution. Equipment used to spray homes include low pressure handwands, and knapsack/backpack sprayers. Applications can be repeated every 90 days.

b-1. Mixer/Loader/Applicator (Handlers) Exposure

Mixer/loader/applicator (i.e., handler) exposure issues are addressed by Subdivision U of the Pesticide Assessment Guidelines. Mixer/loader/applicator (M/L/A) and indoor air residue exposure data were required by the Registration Standard for Products Containing Fenitrothion.

Available data

Mixer/loader/applicator exposure data were required by the Agency because fenitrothion met the triggers for the requirement of exposure data (i.e., toxicity endpoint and the potential for

significant exposure based on the use pattern). The following documents were submitted to the Agency in support of Subdivision U requirements for the reregistration of fenitrothion:

- Safe Use of Pesticides; Third Report of the World Health Organization (WHO) Expert Committee on Vector Biology and Control--Fenitrothion Aspects Excerpted From WHO Technical Report Series 634 (EPA MRID 404089-28),

- Determination of Urinary Metabolites as a Measurement of Exposure of Spraymen and Householders to Fenitrothion and Malathion in Haiti--Presented at the 23rd Meeting of the Collaborative International Pesticide Analytical Council/Sponsored by the Vector Biology and Control Division, Bureau of Tropical Diseases, Centers for Disease Control (EPA MRID 404089-29).

- Exposure of Mixer/Loader/Applicators to Pestroy (Fenitrothion) Insecticide Applied to Ornamentals by Hand-Held Spraygun Equipment (EPA MRID 410963-01). [Note: An addendum was submitted for this study (i.e., MRID 429703-01, Representative Chromatograms and Analytical Data To Supplement Study of Exposure of Mixer/Loader/Applicators to Pestroy (Fenitrothion) Insecticide Applied by Hand-Held Spraygun Equipment, 1988.]

These documents were each reviewed for acceptability by the Agency. To summarize the results of these evaluations, each of the above submissions did not meet the acceptability criteria outlined in Subdivision U of the Pesticide Assessment Guidelines. The WHO and CDC studies were considered unacceptable because of the study design, the level of detail provided therein, and the associated lack of quality control/quality assurance regimens during the biological monitoring of workers. Additionally, the Mixer/Loader/Applicator exposure study is unacceptable (MRID#s 410963-01, 429703-01) because of several major inadequacies.

Exposure estimates

Based on the toxicological endpoints and the significant potential for exposure, fenitrothion continues to meet EPA's criteria for the requirement of mixer/loader/applicator exposure data.

Based on the use patterns described above, several exposure scenarios are plausible as defined by the types of application equipment and procedures that might be employed by fenitrothion handlers. Each scenario is presented in the **Summary Exposure Value** table along with a corresponding exposure assessment (Table 1).

Typical equipment used to treat terrestrial and greenhouse non-food crops and indoor residential targets/crops were considered in this assessment. Basal bark treatments, broadcast applications, and spot treatments can be made using "sprayers", "ground", or "handheld" equipment. Exposure values were calculated based on several sources including: chemical-specific data, the Pesticide Handlers Exposure Database (PHED), and the open literature. All exposure values presented in this RED chapter represent, as closely as possible, the clothing/PPE scenario required for fenitrothion by the Worker Protection Standard (WPS). The WPS requirements include a minimum of coveralls worn over a short-sleeved shirt and short pants, chemical resistant gloves, and a respirator. At a minimum, a disposable dust/mist mask is required with a protection factor of 5.

To clarify the **Summary Exposure Value Table** (Table 1), the **Exposure Scenario Description Table** (Table 2) was developed. Table 2 summarizes the caveats and parameters specific to each exposure scenario.

For several scenarios, exposure data for the exact clothing requirements were not available. As a result, standard protection factors were applied to the available data for each scenario to "normalize" the data in order to represent the WPS clothing scenario as closely as possible . The "clothing scenario" presented in Table 2 indicates the clothing upon which the actual exposure value was developed prior to any "normalization" procedure. The normalization process was based on the following assumptions:

- Unless otherwise indicated, hand exposure accounts for 50 percent of the total dermal exposure while non-hand exposure accounts for the remaining 50 percent,
- Gloves have a protection factor From 50 to 90 percent,
- Normal work clothing (i.e., short-pants and a short-sleeved shirt) has a protection factor of 50 percent,
- Coveralls have a protection factor of 50 percent, and
- Disposable dust/mist masks have a protection factor of 5 (i.e., 80 percent).

Table 1: Summary Exposure Values Which Conform to the WPS Clothing Requirements For Fenitrothion[a]

Exposure Scenario (Scen. #)	Dermal Exposure (mg/lb ai)	Inhalation Exposure (ug/lb ai)	Maximum Label Application Rate[b] (lb ai/cycle)	Daily Maximum Treated[c]	Daily Dermal Exposure[d] (mg/kg/day)	Daily Inhalation Exposure[d] (μg/kg/day)
Mixer/Loader Exposures[e]						
Open Mixing Wettable Powders (I)	0.28	0.48	2 g ai/m^2 or 637 g ai/house (1.40 lb ai)	4 houses	0.022	0.038
Open Mixing Liquids (II)	0.15	0.08	0.03 lb ai/gal	4000 gal/day	0.26	0.14
Applicator Exposures						
Groundboom Application (III)	0.015	0.26	0.03 lb ai/gal	1600 gal/day	0.010	0.18
Low Pressure Handwand Application (IV)	6.0	160.0	0.03 lb ai/gal	120 gal/day	0.31	8.23
Powered Personal Sprayer Application (V)	No Data	No Data	No Data	No Data	No Data	No Data
Overhead Boom Sprayer Application (VI)	7.65 mg/gal	No Data	0.17 lb ai/gal	120 gal/day	13.11	No Data
Liquid Broadcast Spreader Application (VII)	No Data	No Data	No Data	No Data	No Data	No Data
High Pressure Handwand Application (VIII)	0.12	0.018	0.03 lb ai/gal	2000 gal/day	0.10	0.015
Mixer/Loader/Applicator Exposures						
Mixing and Application with Low Pressure Handwands (IX)	51.5	7.8	0.03 lb ai/gal	120 gal/day	2.65	0.40
Knapsack/ Backpack Application (X)	1.93	6.04	0.03 lb ai/gal	240 gal/day	0.20	0.62
Mixing and Application with High Pressure Handwand (XI)	0.52	3.94	0.03 lb ai/gal	2000 gal/day	0.45	3.38

a Exposure units may differ from those defined in headers because of the type of equipment used. Alternate units are noted where appropriate. All unit exposure values reflect the WPS clothing/PPE requirements for fenitrothion which is a toxicity II dermal and inhalation pesticide (i.e., WPS = coveralls worn over short-sleeved shirt and short pants, protective gloves, and a minimum PF5 respirator which is typically considered a disposable dust/mist mask).

b Values represent the maximum application rate allowable by the label. Mixing/loading scenarios were based on the highest rate for **all** application methods included in this table (e.g., for Open Mixing Liquids, the daily exposure levels were calculated based on a mixer/loader supporting 2 high pressure handwand sprayers per day).

c Values represent the maximum area or the maximum spray solution volume which can be used in one day to complete treatments for a each equipment type/exposure scenario of interest.

d Daily Exposure (μg or mg/kg/day) = [(Exposure (μg or mg/lb ai) * Max. Appl. Rate (lb ai/cycle) * Max. Treated)/70 kg]

e Reported mixer/loader exposure levels represent the maximum amount of chemical which can be handled on a daily basis. Therefore, the resultant exposure values cannot be directly added to exposure values for each application technique.

Table 2: Exposure Scenario Descriptions For Fenitrothiona

Exposure Scenario (Scen. #)	Data Source	Clothing Scenario	Equipment	Formulation	Standard Assumptions[b] (8 hr workday)	Comments[c]
Mixer/Loader Exposures[d]						
Open Mixing Wettable Powders (I)	PHED	Long Pants, Short Sleeves, No Gloves	Open System	Wettable Powders in Bags (i.e., water soluble packets **not** included)	4 houses/day, 637 g ai/house, 50% protection factor applied to both hand and dermal (nonhand) exposure to account for the use of protective gloves and a coverall	Only WP use is mosquito control, (grams ai) based on typical house in U.S.,[11,12] Poor quality control for some datapoints
Open Mixing Liquids (II)	PHED	Long Pants, Long Sleeves, No Gloves	Open System	All liquids	See high pressure handwand below, 50% protection factor applied to both hand and dermal (nonhand) exposure to account for the use of protective gloves and a coverall	Mixer/loader can support 2 applicators on a daily basis. Exposure/MOE value calculated only for the maximum use scenario.
Applicator Exposures						
Groundboom (III)	PHED	Long Pants, Long Sleeves, No Gloves	Open Cab Groundboom Tractor	All Formulations	200 gallons/hour, 8 hour day, 50% protection factor applied to both hand and dermal (nonhand) exposure to account for the use of protective gloves and a coverall	n = 6-77; 65% of data with grades A,B,C; Hands mostly (50%) D,E.
Low Pressure Handwand (IV)	PHED	Long Pants, Long Sleeves, No Gloves	Low Pressure Handwand	All Formulations	6 tankloads/hour, 8 hour day, 2.5 gallon/tank, 50% protection factor applied to both hand and dermal (nonhand) exposure to account for the use of protective gloves and a coverall	n = 9-13 (i.e. inadequate # of reps); all reps C grade data
Powered Personal Sprayer (V)	No Data	No Data	No Data	No Data	No Data	No Data
Overhead Boom Sprayer (VI)	Haverty, et al 1983	Total Deposition	Hudson Stirrup Garden Pump with telescoping overhead pole	Sevimol (Carbaryl) addended with Rhodamine B Dye	@ 2 gal/tree, @ 1 tank/tree, 6 tanks/hour, 8 hour day, 2.5 gallon tank, 50% protection factor applied twice to dermal exposure data to account for personal clothing and the use of a coverall, also, 50% protection factor was applied to account for the use of protective gloves	No QA/AC data; application technique similar to low pressure handwand with telescope boom[4,5]
Liquid Broadcast Spreader (VII)	No Data	No Data	No Data	No Data	No Data	No Data

Table 2: Exposure Scenario Descriptions For Fenitrothion[a] (continued)

Exposure Scenario (Scen. #)	Data Source	Clothing Scenario	Equipment	Formulation	Standard Assumptions[b] (8 hr workday)	Comments[c]
High Pressure Handwand (VIII)	PHED	Long pants, long sleeves, gloves	High Pressure Handwand on Wheels	All Formulations	250 gallons/hour, 8 hours/day, 50% protection factor applied to dermal (nonhand) exposure to account for coverall over the personal clothing	Grade B and C data, n = 9 (i.e., inadequate number of reps)
Mixer/Loader/Applicator Exposures						
Mixing and Application with Low Pressure Handwand (IX)	PHED	Long Pants, Long Sleeves, No Gloves	Low Pressure Handwand	All Formulations	6 tankloads/hour, 8 hour day, 2.5 gallon/tank, 50% protection factor applied to both hand and dermal (nonhand) exposure to account for the use of protective gloves and a coverall	n = 25-95; dermal grades B, C, E, hands, inhalation = B,C data.
Knapsack/ Backpack (X)	PHED	Long Pants, Long Sleeves, Gloves	Backpack	All Formulations	6 tankloads/hour, 8 hour day, 5 gallon tank, 50% protection factor applied to dermal (nonhand) exposure to account for coverall over the personal clothing	n = 9; dermal B; airborne B; Hands (gloves) C: (i.e., inadequate number of reps)
Mixing and Application with High Pressure Handwand (XI)	MRID #s 410963-01 & 429703-01	Long Pants, Long Sleeves, Gloves	High Pressure Handwand (Nursery Type)	Pestroy 8E	250 gallons/hour, 8 hour day, open mixing operations, 50% protection factor applied to dermal (nonhand) exposure to account for coverall over the personal clothing	QA/QC data inadequate. Did not meet Sub U criteria, did not adhere to PPE recommended on label; no storage stability data.

a "No Data" indicates that no data were available to complete an exposure assessment.
b Standard Assumptions based on an 8 hour work day as estimated by OREB. BEAD data were not available.
All standard assumptions based on the maximum application rate allowable by specific product labels.
c Only comments pertaining to poor quality data are included pertaining to the reliability of each exposure scenario (i.e., no comments regarding high quality data are included).
All other pertinent comments are also included in this column of the table, as appropriate.
d Mixer/Loader exposures are not appropriate for all equipment scenarios as indicated in the above table. Mixer/loader exposure values are calculated based only on the maximum use application scenario
(i.e., the application method for which the most chemical can be used on a daily basis).

b-2 Post-application/Reentry Exposure (Worker and Residential) and REI

Post-application exposure issues (i.e., reentry) are addressed by Subdivision K of the Pesticide Assessment Guidelines. Fenitrothion met the triggers for the requirement of post-application exposure/residue dissipation data on the basis of toxicity endpoint and the potential for significant exposure based on the use pattern. Consequently, foliar residue dissipation along with post-application dermal and inhalation exposure data were required in the Registration Standard for Products Containing Fenitrothion[1] issued in September, 1987.

Available data

All available data were submitted by the registrant. However, they are inadequate to calculate a reliable Restricted Entry Interval (REI) for any of the appropriate use sites described above for fenitrothion.

Exposure estimates

Specifically, the following post-application exposure scenarios are of concern to the Agency.

Indoor Uses

- Residential exposure after mosquito control treatments. [Note: Potential inhalation exposure is 427 mg over the course of a 15 hour day (i.e., 28.46 mg/hr) in a typical treated residence. See below for explanation of these values.]

- Greenhouse worker exposure after treatment of ornamental plant beds and potted plants.

Outdoor Uses

- Exposure after contact with treated ornamental plants and foliage.

Available data

Post-application Exposure Estimates

The following documents were submitted to the Agency by the registrant in support of Subdivision K requirements for the reregistration of fenitrothion applied to outdoor sites:

- Potential for Re-Entry Exposure to Sumithion

(Fenitrothion) 8E Insecticide Used on Ornamentals: A Review of All Registered Uses (MRID 407430-01), and

- Risk Assessment Based on Surrogate Exposure Models For Workers Reentering Elms Treated with Fenitrothion Insecticide/Miticide (MRID 407430-02).

These documents were each reviewed for acceptability by the Agency. To summarize the results of these evaluations, each of the above submissions did not meet the acceptability criteria outlined in Subdivision K of the Pesticide Assessment Guidelines. For the determination of exposure potential no actual exposure data were generated in either of these studies. Several inadequacies were identified in the studies. Both studies were theoretical determinations of exposure potential based solely on a subjective assessment of agricultural and pesticide application practices. Furthermore, adequate QA/QC data were not included. Finally, the determination of the leaf area of elm saplings was inconclusive; the estimation of fenitrothion half-life in the report was not justified; and inhalation exposure potential was ignored.

Exposure estimate

Based on the toxicological endpoints and the significant potential for exposure, fenitrothion may continue to meet EPA's criteria for the requirement of post-application exposure/residue dissipation data.

The calculation of the projected indoor inhalation exposure levels for the residential malaria control use of fenitrothion is summarized below.

! ASTM Standard E 1333-90 indicates that the relationship between house volume and wall sufrace is:
$0.95 m^2$ wall area/m^3 of house volume

! Geomet test house in which the same relationship based on empirical evidence is:
$1.37 m^2$ wall area/m^3 of house volume

! Average house volume in the U.S. can be calculated based on the Statistical Abstract of the United States, 1982. These calculations are outlined below:

Distribution of residence types
(1) 65% single family units (i.e., SF houses & townhouses)
(2) 35% apartment/mobile homes

Square Footage/Volume of Building Types
(1) 1900 ft^2 (176.5m^2) X 7.5 ft (2.86m) ceilings = 403.5 m^3

Weighted Average
((65 X 403.48) + (350 X 208)0/100 = 335m^3

Average Wall Surface Area can be calculated as follows:

335m^3 avg. house volume X 0.95m^2 wall surface/m^3 house volume = 318.25 m^2

Average linear Feet of Baseboard/House can be calculated as follows:
318.25 m^2 wall surface area/2.286m avg. wall height - 139.22m of baseboard

Average Application Rate (grams ai) for a Typical Home can be calculated as follows:
318.25m^2 wall space X Application Rate (2 g ai/m^2 wall space) = 637 g ai

Theoretical Airborne Concentration (Assuming 1% Volatilization) can be calculated as follows:
(617 grams ai/house X 0.01 (i.e. 1%))/335 m^3 of house volume = 19.01 mg ai/m^3

Potential Inhalation Exposure (mg ai/15 hour daily residential interval) can then be calculated as follows:
19.01 mg/ai/m^2 volume X 25 Lpm avg. inhalation rate X 15 hr. X 60 min./hr. X 1m^3/1000 l = 427 mg exp./15 hr. daily exposure interval (i.e., 28.46 ai/hr.)

Recommendations

Restricted Entry Interval

The Registration Standard (1987) established an interim reentry interval of 24 hours for fenitrothion for all applicable uses until adequate reentry data became available. Additionally, the Worker Protection Standard (WPS) for Agricultural Pesticides (40CFR156) established a 12-hour Restricted-Entry Interval (REI). However, based on the currently available toxicology data for reregistration, it appears that this interim 12-hour REI presented in the WPS for fenitrothion is inadequate. The REI should be at least 24 hours since fenitrothion is Toxicity category II for dermal toxicity, which, in accordance with the WPS, at a minimum requires a 24-hour REI). The Agency recommends continuing to require a 24-hour REI for all use sites within the scope of the WPS until adequate post-application exposure data are submitted.

Personal Protective Equipment (PPE) Requirements

PPE selection for mixer/loader/applicators and other handlers will be based on the end-use product. The following statements to be included on fenitrothion labels are located on the Pesticide Worksheets -- Parts One and Two: **Reduced PPE When Engineeering Controls Used**; **User Safety Statements**; **Application Restrictions**; **Entry Restrictions**; **Early-Entry PPE**; and **Notification Statements** (see attachment I).

Except for homeowner users, the Agency is requiring PPE for applicators and other handlers as well as early entry workers consistent with the PPE level required for pesticides classified as Toxicity Category II for acute dermal toxicity (40 CFR Part 156, the Worker Protection Standard). For further information see PR Notices 93-7 and 93-11.

3. Risk Assessment

a. Dietary

a-1. Toxicological Endpoints

Chronic exposure calculated in this analysis was compared to a Reference Dose (RfD) of 0.0013 mg/kg body weight/day, based on a No-Observed-Effect-Level (NOEL) of 0.125 mg/kg bwt/day and an Uncertainty Factor of 100. The NOEL was taken from a one year feeding study in dogs which demonstrated plasma cholinesterase inhibition and lymph node hemorrhaging.

a-2. Residue parameters

There are no food uses of fenitrothion currently registered which are subject to reregistration by the Agency under FIFRA. A tolerance exists in 40 CFR 185.2200(a) for residues of fenitrothion and two of its metabolites in wheat gluten resulting from postharvest application of the insecticide to stored wheat in Australia. This is the only food use present in the DRES file for this chemical.

The HED Metabolism Committee has concluded that only fenitrothion **per se** needs to be regulated in wheat gluten (B. Cropp-Kohlligian memo, 2/24/93); the Residue Chemistry Chapter recommends that the tolerance expression for residues of fenitrothion be amended to specify fenitrothion only at 15 ppm. In the DRES analysis, the existing tolerance of 30 ppm was entered as the tolerance and the recommended tolerance of 15 ppm was entered as an anticipated residue.

The DRES system does not specifically have a consumption estimate for "wheat gluten." The closest category in DRES is "wheat flour." In an effort to get a more realistic consumption estimate for wheat gluten, an estimate of the amount of wheat gluten imported from Australia was requested from BEAD. According to USDA, all wheat gluten consumed in the United States is imported; around 40,000 metric tons of wheat gluten are imported into this country annually, with about 40 percent of this coming from Australia. Using these estimates, assuming that the U.S. population is approximately 255,462,000 (1992 Census), and assuming the average body weight of the U.S. population to be 58.9 kg (the mean body weight of respondents in the 1977-78 Nationwide Food Consumption Survey, from which DRES consumption estimates are derived), a consumption estimate for Australian wheat gluten of 0.002913 g/kg bwt/day was calculated. By comparing this consumption estimate to that for flour (1.2572489 g/kg bwt/day), a

conversion factor of 0.23, reflecting gluten consumption as a percentage of wheat flour consumption, was derived and used in the DRES analysis.

A summary of the residue information used in the DRES analysis is attached in Attachment IV.

a-3. Dietary Risk

Using the derived wheat gluten consumption estimate and the recommended residue of 15 ppm, exposure to the overall U.S. population was estimated at 0.000043 mg/kg bwt/day, which represents 3% of the RfD. If one assumes that wheat gluten is consumed by children at the same ratio to the overall U.S. population's consumption that wheat flour is, the estimated exposure for children one through six is 0.000097 mg/kg bwt/day, or 8% of the RfD. If the existing tolerance of 30 ppm is used, these exposure and risk estimates are doubled (7% of the RfD for the overall U.S. population, 15% of the RfD for children 1 through 6). The risk calculations performed to get these estimates are included in Attachment IV.

The acute neurotoxicity endpoint is appropriate for dietary risk assessment. However, because Australian gluten is probably mixed with other gluten, there is not likely to be an acute risk from gluten consumption. Calculations using the RfD indicate minimal risk; since the acute NOEL is 100-fold greater than the NOEL used to establish the RfD, there is no concern for acute dietary exposure.

b. Occupational and Residential

<u>Toxicological endpoints</u>

HED has a concern for brain, RBC and plasma ChE inhibition associated with exposure to fenitrothion. These effects were observed in subchronic studies.

In a 21-day dermal study (Guideline requirement 82-2) MRID No. 420583-01 Fenitrothion (93.7%), the Systemic NOEL equals 3 mg/kg/day, and the Systemic LOEL equals 10 mg/kg/day based on inhibition of plasma cholinesterase (40%) and brain (20%) cholinesterase in females. The dermal NOEL was not determined. The dermal LOEL equals 3 mg/kg/day based on dermal irritation and desquamation of the epidermis.

In a 90 day inhalation study (Guideline requirement 82-4) MRID No. 408910-01 Crl (WI) BR strain rats were exposed to 0, 0.2, 1.0,

or 10 µg/l of Sumithion Technical (94.5%). Cholinesterase was inhibited in females at all exposure levels). At 10 µg/l, plasma Cholinesterase activity in males and RBC Cholinesterase activity in both males and females was inhibited. Brain Cholinesterase was inhibited only in females at 1 or 10 µg/l. A NOEL of 0.2 μg/l was determined on the basis of Brain Cholinesterase inhibition in females.

Occupational and Residential risk

There is a potential risk from dermal and inhalation exposure to mixer/loaders and applicators. There is a potential for inhalation exposure upon reoccupation/reentry of treated (painted) homes. The exposure, due to off-gassing, may be acute (residents and workers), intermittent (workers during their working life span), or chronic (residents and workers). The registrant has not provided previously requested post-application air monitoring data for off-gassing.

Margins of exposure may be calculated from:

$$MOE = \frac{NOEL}{exposure}$$

- where the NOEL equals 3 mg/kg/day for dermal exposure; and
- where the NOEL equals 0.049 mg/kg/day for inhalation.

The NOEL for inhalation is 0.2 µg/l. Acute, subchronic, and chronic inhalation exposures of residents and workers reentering painted houses after aeration may be estimated using the following equation:

$$mg/kg/day = \frac{PPM \times MW}{24450} \times \frac{resp.\ vol.\ (liters/day)}{Kg\ body\ weight}$$

See Appendix I for the derivation of this value. Table 3 gives MOE estimates for all the exposure scenarios in Table 1.

Table 3: MOE estimates of potential neurotoxicity to workers

Exposure Scenario (Scen. #)	Daily Dermal Exposure[d] (mg/kg/day)	Daily Inhalation Exposure[d] (μg/kg/day)	Intermediate MOE		Chronic MOE Inhalation
			Dermal	Inhalation	
Mixer/Loader Exposures[f]					
Open Mixing Wettable Powders (I)	0.022	0.038	140	1289	1289
Open Mixing Liquids (II)	0.26	0.14	12	350	350
Applicator Exposures					
Groundboom Application (III)	0.010	0.18	300	272	272
Low Pressure Handwand Application (IV)	0.31	8.23	10	6	6
Powered Personal Sprayer Application (V)	No Data	No Data	N/A	N/A	N/A
Overhead Boom Sprayer Application (VI)	13.11	No Data	0.23	213	213
Liquid Broadcast Spreader Application (VII)	No Data	No Data	N/A	N/A	N/A
High Pressure Handwand Application (VIII)	0.10	0.015	30	327	327
Mixer/Loader/Applicator Exposures					
Mixing and Application with Low Pressure Handwands (IX)	2.65	0.40	1	123	123
Knapsack/ Backpack Application (X)	0.20	0.62	15	79	79
Mixing and Application with High Pressure Handwand (XI)	0.45	3.38	7	14	14
Post Application Exposure					
Mosquito Control (Residential)	N/A	427 mg for 15 hours (6.1 mg/kg/day)	N/A	N/A	0.008

a Exposure units may differ from those defined in headers because of the type of equipment used. Alternate units are noted where appropriate. All unit exposure values reflect the WPS clothing/PPE requirements for fenitrothion which is a toxicity II dermal and inhalation pesticide (i.e., WPS = coveralls worn over short-sleeved shirt and short pants, protective gloves, and a minimum PF5 respirator which is typically considered a disposable dust/mist mask).

b Values represent the maximum application rate allowable by the label. Mixing/loading scenarios were based on the highest rate for **all** application methods included in this table (e.g., for Open Mixing Liquids, the daily exposure levels were calculated based on a mixer/loader supporting 2 high pressure handwand sprayers per day).

c Values represent the maximum area or the maximum spray solution volume which can be used in one day to complete treatments for a each equipment type/exposure scenario of interest.

d Daily Exposure (μg or mg/kg/day) = [(Exposure (μg or mg/lb ai) * Max. Appl. Rate (lb ai/cycle) * Max.

Treated)/70 kg]
e Dermal/inhalation MOE values calculated using the following equation: MOE = NOEL/Exposure; 21 day dermal NOEL = 3 mg/kg/day (MRID 420583-01); 90 day inhalation (for intermediate and chronic) NOEL = 49 µg/kg/day or .049 mg/kg/day.
f Reported mixer/loader exposure levels represent the maximum amount of chemical which can be handled on a daily basis. Therefore, the resultant exposure
values cannot be directly added to exposure values for each application technique. Any additional daily exposure levels of interest must be hand calculated.

For the following exposure scenarios the MOEs are less than 100:

- Residential exposure after mosquito control treatments
- Open mixing liquids (mixer/loader);
- Low pressure handwand application (applicator);
- Overhead boom sprayer application (applicator);
- High Pressure handwand application (applicator);
- Mixing and application with low pressure handwands (mixer/loader/applicator);
- Knapsack/backpack (mixer/loader/applicator); and
- Mixing and application with high pressure handwand (mixer/loader/applicator).

Data Gaps

There are no exposure data to support powered personal sprayer and liquid spreader application. For these uses, a MOE calculation was not possible. These application techniques are not eligible for reregistration. Mixer/loader/applicator low and high pressure handwand, overhead boom, and knapsack/backsack data (Guideline 231 and 232) are required to support these uses. Air monitoring data for residential exposure after mosquito control also are still required.

The following toxicology data gaps exist: 1) inhalation acute LC_{50} study; and 2) six-month ocular toxicity study in the dog.

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Appendix I

Acute, subchronic, and chronic inhalation exposures of residents and workers reentering painted houses after aeration may be estimated using the following equation and assumptions:

$$\text{mg/kg/day} = \frac{\text{PPM X MW}}{24450} \text{ X } \frac{\text{resp. vol. (liters/day)}}{\text{Kg body weight}}$$

Assumptions:

- **!** Molecular weight Fenitrothion = 277.2
- **!** Adult body weights (see table)
- **!** Wistar rat values are equivalent to Sprague Dawley
- **!** Respiratory volume (resp. vol.) based on 16 hours rest + 8 hours light work [ventilation rates (L/min) are respectively for humans 7.4 (M) and 4.5 (F) at rest and 29 (M) and 16 (F) with light work
- **!** Rat Respiratory volume (resp. vol.) not adjusted for rest or work
- **!** 100% pulmonary absorption
- **!** LEL value of .2 μg/l, based on plasma ChE activity inhibition in female rats
- **!** NOEL value of .2 μg/l, based on brain ChE activity in female rats (see 82-4 above)
- **!** The NOEL is 0.2 μg/l based on the 90-day inhalation toxicity study, which may be the most appropriate NOEL for determining acute, subchronic, and chronic exposure
- **!** As the rat exposure is only 6 hours divide the rat 24 hour respiratory volume by 4

Table 3 - assumptions used in PPM to Mg/kg/day conversions

Species - Strain	Respiratory Vol/24 hr (m^3/24hr)		Body Weight (Kg)	
	♂		♂	♀
Rat-Fisher	0.37	0.26	0.4	0.25
Sprague Dawley	0.50	0.34	0.6	0.35
Homo Sapiens	21.024	12.0	70.0	68.5
Rabbit-NZW	1.49		4.1	

Values taken from EPA RfC workshop committee, RTP.

Converting μg/ to mg/l 0.2 μg/l X $\frac{1\text{mg}}{1000\ \mu\text{g}}$ = 0.0002 mg/l

Respiratory Rate Vol/24 hr for SD ♀ rats = 0.34 m^3 = 340 liters
Volume for 6 hours = 0.085m^3 = 85 liters

Female Rat: mg/kg/day = 0.0002 mg/l X $\frac{85\ l}{0.35\ kg}$ = 0.049

The female rat value of 0.049 mg/kg/day is the value used in the MOE risk assessment for this route of exposure.

Human: mg/kg/day = $\frac{427\ mg/day}{70.0\ kg}$ = 6.1 mg/kg/day
Human (♀)
Deposition